EXHIBIT A

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Original Investigation

Use of Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction and Risk of Malignant Melanoma

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IMPORTANCE The target for the oral erectile dysfunction drugs, phosphodiesterase type 5 (PDE5) inhibitors, is part of a pathway implicated in the development of malignant melanoma. An increased risk of melanoma in sildenafil users was recently reported.

OBJECTIVE To examine the association between use of PDE5 inhibitors and melanoma risk, including data on specific PDE5 inhibitors, number of prescriptions, and melanoma stage.

DESIGN, SETTING, AND PARTICIPANTS Nationwide, population-based, nested case-control study in the Swedish Prescribed Drug Register, the Swedish Melanoma Register, and other health care registers and demographic databases in Sweden, including 4065 melanoma cases diagnosed from 2006 through 2012 and 5 randomly selected controls per case with matching year of birth.

EXPOSURES Number of filled prescriptions for the PDE5 inhibitors sildenafil and vardenafil or tadalafil.

MAIN OUTCOMES AND MEASURES Risk of melanoma; overall and by stage and risk of basal cell carcinoma in multivariable logistic regression analyses.

RESULTS Of 4065 melanoma cases, 435 men (11%) had filled prescriptions for PDE5 inhibitors, as did 1713 men of 20 325 controls (8%). In multivariable analysis, there was an increased risk of melanoma in men taking PDE5 inhibitors (OR, 1.21 [95% CI, 1.08-1.36]). The most pronounced increase in risk was observed in men who had filled a single prescription (OR, 1.32 [95% CI, 1.10-1.59]; exposure rate, 4% for cases vs 3% for controls), but was not significant among men with multiple filled prescriptions (for 2-5 prescriptions: OR, 1.14 [95% CI, 0.95-1.37], 4% for cases and 3% for controls; for ≥6 prescriptions: OR, 1.17 [95% CI, 0.95-1.44], 3% for cases vs 2% for controls). PDE5 inhibitors were significantly associated with melanoma stage 0 (OR, 1.49 [95% CI, 1.22-1.83], 13% for cases vs 8% for controls) and stage I (OR, 1.21 [95% CI, 1.02-1.43], 12% for cases vs 10% for controls), but not stage II through IV (OR, 0.83 [95% CI, 0.63-1.09], 6% for cases vs 7% for controls). The risk estimates were similar for sildenafil and vardenafil or tadalafil. PDE5 inhibitor use was also associated with an increased risk of basal cell carcinoma (OR, 1.19 [95% CI, 1.14-1.25], 9% for cases vs 8% for controls). Men taking PDE5 inhibitors had a higher educational level and annual income, factors that were also significantly associated with melanoma risk.

CONCLUSIONS AND RELEVANCE In a Swedish cohort of men, the use of PDE5 inhibitors was associated with a modest but statistically significant increased risk of malignant melanoma. However, the pattern of association (eg, the lack of association with multiple filled prescriptions) raises questions about whether this association is causal.

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Phosphodiesterase type 5 (PDE5), the target of oral erectile dysfunction drugs, is part of the RAS-RAF-MEK-ERK signaling pathway that has been implicated in the development of malignant melanoma. Specifically, mutations in the *BRAF* gene lead to down-regulation of PDE5, which increases cytosolic calcium via cyclic guanosine monophosphate, which ultimately increases the invasiveness of melanoma cells.[1] This has raised questions regarding whether PDE5 inhibitors used to treat erectile dysfunction promote malignant melanoma through a similar mechanism.

An increased risk of melanoma of the skin following sildenafil use was recently reported in a US cohort study based on 14 cases of malignant melanoma among men taking PDE5 inhibitors (recent use: hazard ratio [HR], 1.84 [95% CI, 1.04-3.22]; ever use: HR, 1.92 [95% CI, 1.14-3.22]).[2] Following this report, it has been suggested that PDE5 inhibitors represent an important part of the medical history for dermatologists, and that melanoma screening could be performed by the physician when a sildenafil prescription is written for an older man with a history of sunburns.[3,4]

It is projected that by 2025, 322 million men worldwide will be affected by erectile dysfunction,[5] and PDE5 inhibitors are the most commonly prescribed medications used for treatment of this condition.[6] Given the frequency with which these medications are used, further support for a causal association with the development of malignant melanoma would have important implications.

The objective of this study was to reexamine the association between use of PDE5 inhibitors and malignant melanoma using population-based data in the Swedish Prescribed Drug Register, the Swedish Melanoma Register, and other nationwide health care registers and demographic databases in Sweden. We hypothesized that if PDE5 inhibitors promote malignant melanoma[7]: (1) men with the greatest number of prescriptions would have the highest risk, (2) PDE5 inhibitors with longer half-life would be associated with higher risk (ie, a dose-response relationship), (3) there would be a higher risk of advanced-stage melanoma in users of PDE5 inhibitors, and (4) there would be no association between PDE5 inhibitors and basal cell carcinoma in which the implicated pathway is not involved.[2]

Methods

The Research Ethics Board at Umeå University Hospital approved the study and it received exempt status for participant consent. We performed a nested case-control study to examine the association between PDE5 inhibitors and the risk of malignant melanoma. By use of the unique Swedish person identity number, the comparison cohort of the Prostate Cancer Data Base Sweden (PCBaSe 3.0) was linked with the Swedish Cancer Registry. The 614 601 prostate cancer-free comparison group in PCBaSe had been randomly selected from the Swedish population on a 1:5 ratio from groups of men matching the prostate cancer cases on year of birth and county of residency. We identified incident melanoma cases diagnosed between 2006 and 2012, who were free of other cancers at the date of melanoma diagnosis. For each case of malignant melanoma, we randomly selected 5 controls using incidence density sampling, stratified on year of birth from men who were cancer-free at the date of diagnosis for the index case.[8]

The Swedish Melanoma Register was used to obtain detailed information on location and stage for melanoma cases, which were then categorized into early stage: stage 0 (melanoma in situ, not N1 or M1), intermediate stage, stage I (Breslow thickness ≤1 mm, not N1 or M1), and advanced stage II through IV (Breslow thickness >1 mm or N1 or M1).[9]

In a separate analysis, we also examined the association between use of PDE5 inhibitors and risk of basal cell carcinoma of the skin. Information on basal cell carcinoma was retrieved from a separate section of the Swedish Cancer Registry that is dedicated to this diagnosis. We identified incident basal cell carcinoma cases diagnosed between 2006 and 2012, who were free of other cancers at the date of basal cell carcinoma diagnosis. For each case, 2 controls were randomly selected using incidence density sampling, stratified on birth year, from men who were cancer-free at the date of diagnosis for the index case.

The Swedish Prescribed Drug Register, which includes data on all prescribed medications since July 2005, was used to determine the number of filled prescriptions for PDE5 inhibitors.[10] Therefore, only cases diagnosed in 2006 (ie, the first full year with availability of prescription data) or later were included in the study of melanoma and basal cell carcinoma.

We examined the relationship between the number of filled PDE5 inhibitor prescriptions (1, 2-5, ≥6) and melanoma risk. Separate analyses were performed to examine specific PDE5 inhibitors (sildenafil and vardenafil or tadalafil with a longer half-life[11]), and stage of melanoma at diagnosis.

Data on educational level, income, and marital status were obtained from the LISA database, a longitudinal integration database for health insurance and labor market studies. Data from the Patient Register on discharge diagnosis (*International Classification of Diseases, Tenth Revision* coding) from hospital admissions up to 10 years prior to the date of melanoma diagnosis for cases, and for controls the date for their index case, were used to calculate a Charlson comorbidity index (CCI).[12] This index is a weighted score, based on the sum of 17 categories of diagnoses as previously described.[13]

Multivariable conditional logistic regression analyses were performed to estimate odds ratios (ORs) adjusting for CCI, marital status (married vs not married, divorced, separated, or widowed), educational level (low, <10 years; intermediate, 10-12 years; high, >12 years including university education or equivalent) and disposable income. Similar models were performed for preplanned subset analysis of men younger than 70 years at the time of melanoma diagnosis. Subset analysis was also performed to estimate ORs for melanoma in men exposed to PDE5 inhibitors within 1 year and more than 1 year prior to diagnosis. A complete-case analysis was performed as there was less than 2% missing data overall. Data management and incidence density sampling were performed using Statistical Analysis Systems

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Table 1. Demographics for Cases and Controls in a Nested Case-Control Study of Malignant Melanoma

	Men With Filled PDE5 Inhibitor Prescriptions, No. (%)			Men Without Filled PDE5 Inhibitor Prescriptions, No. (%)		
	Cases (n = 435)	Controls (n = 1713)	All Men (n = 2148)	Cases (n = 3630)	Controls (n = 18 612)	All Men (n = 22 242)
Age, median (IQR), y	69 (65-74)	70 (65-75)	70 (65-75)	75 (69-82)	75 (68-81)	75 (68-81)
<60	29 (7)	109 (6)	138 (6)	147 (4)	772 (4)	919 (4)
60-69	198 (46)	712 (42)	910 (42)	848 (23)	4478 (24)	5326 (24)
70-79	169 (39)	759 (44)	928 (43)	1455 (40)	7427 (40)	8882 (40)
≥80	39 (9)	133 (8)	172 (8)	1180 (33)	5935 (32)	7115 (32)
Comorbidity[a]						
CCI 0	355 (82)	1327 (77)	1682 (78)	2463 (68)	12 111 (65)	14 574 (66)
CCI 1	58 (13)	206 (12)	264 (12)	588 (16)	3084 (17)	3672 (17)
CCI 2+	22 (5)	180 (11)	202 (9)	579 (16)	3417 (18)	3996 (18)
Marital status						
Not currently married	131 (30)	581 (34)	712 (33)	1120 (31)	6877 (37)	7997 (36)
Married	304 (70)	1127 (66)	1431 (67)	2508 (69)	11 717 (63)	14 225 (64)
Missing data	0	5 (<1)	5 (<1)	2 (<1)	18 (<1)	20 (<1)
Educational level[b]						
Low	100 (23)	586 (34)	686 (32)	1352 (37)	8482 (46)	9834 (44)
Middle	166 (38)	655 (38)	821 (38)	1352 (37)	6367 (34)	7719 (35)
High	165 (38)	455 (27)	620 (29)	887 (24)	3442 (18)	4329 (19)
Missing data	4 (1)	17 (1)	21 (1)	39 (1)	321 (2)	360 (2)
Annual income, percentiles						
1-25	47 (11)	269 (16)	316 (15)	741 (20)	5040 (27)	5781 (26)
26-50	63 (15)	315 (18)	378 (18)	878 (24)	4827 (26)	5705 (26)
51-75	131 (30)	471 (28)	602 (28)	961 (27)	4527 (24)	5488 (25)
76-100	193 (44)	653 (38)	846 (39)	1043 (29)	4155 (22)	5198 (23)
Missing data	1 (<1)	5 (<1)	6 (<1)	7 (<1)	63 (<1)	70 (<1)

Abbreviations: CCI, Charlson comorbidity index, IQR, interquartile range; PDE5, phosphodiesterase type 5.

[a] CCI 0 indicates no comorbidity; CCI 1, mild comorbidity; CCI 2+, moderate to severe comorbidity.

[b] Educational levels: low, compulsory school (< 10 years); middle, upper secondary school (10-12 years); high, college or university (>12 years).

(SAS Institute), version 9.2. R (R Foundation for Statistical Computing), version 3.1.1, was used for statistical analysis. The significance level was set to a *P* value less than .05 and all tests were 2-sided.

Results

A total of 4065 previously cancer-free men were diagnosed with melanoma during the study period (cases) and were compared with 20 325 cancer-free men (controls). **Table 1** shows the demographics of the study population, and **Table 2** shows melanoma features. Men who had filled prescriptions for PDE5 inhibitors were younger, had less comorbidities, were more often married, had a higher educational level, and had a higher income than men without PDE5 inhibitor prescriptions. Among men who had filled PDE5 inhibitor prescriptions, those diagnosed with melanoma had a lower CCI, higher educational level, and higher income than men not diagnosed with melanoma.

Of 4065 melanoma cases, 435 men (11%) had filled prescriptions for PDE5 inhibitors, as did 1713 men of 20 325 controls (8%) (crude OR, 1.31 [95% CI, 1.17-1.47]). In multivariable analysis, a significantly increased risk of melanoma remained in men with filled PDE5 inhibitor prescriptions (OR, 1.21 [95% CI, 1.08-1.36]).

Among users of PDE5 inhibitors, 734 men (34%) had filled a single prescription, 804 men (37%) had 2 through 5 prescriptions, and 610 men (28%) had filled 6 or more prescriptions (eTable 1 in the Supplement). In multivariable analysis, the risk of melanoma was significant for men who had filled a single prescription (OR, 1.32 [95% CI, 1.10-1.59]; 4% for cases vs 3% for controls) but not for men with multiple filled prescriptions (for 2-5 prescriptions: OR, 1.14 [95% CI, 0.95-1.37], 4% for cases vs 3% for controls; for ≥6 prescriptions: OR, 1.17 [95% CI, 0.95-1.44], 3% for cases vs 2% for controls) (**Table 3**). There was also a significantly increased risk of melanoma among married men, those with a higher educational level, and those with a higher annual income; men with a CCI of 2 or higher were significantly less likely to be diagnosed with melanoma.

PDE5 inhibitors were significantly associated with stage 0 (OR, 1.49 [95% CI, 1.22-1.83]; 13% for cases vs 8% for controls) and stage I melanoma (OR, 1.21 [95% CI, 1.02-1.43]; 12% for cases vs 10% for controls), but not with stages II through IV (OR, 0.83 [95% CI, 0.63-1.09]; 6% for cases vs 7% for con-

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Table 2. Malignant Melanoma Characteristics for Cases by Phosphodiesterase Type 5 Inhibitor Exposure

	No. (%)	
	Exposed (n = 435)	Unexposed (n = 3630)
Pathologic stage[a]		
0	153 (35)	1037 (29)
IA	33 (8)	320 (9)
IB	78 (18)	621 (17)
Ix	97 (22)	561 (15)
II	63 (14)	951 (26)
III-IV	5 (1)	96 (3)
Missing data	6 (1)	44 (1)
Location		
Head or neck	71 (16)	838 (23)
Torso	119 (27)	917 (25)
Extremities	237 (54)	1825 (50)
Missing data	8 (2)	50 (1)

[a] Pathologic stage was defined based on Breslow thickness (mm), ulceration status, mitotic rate, and biopsies of lymph nodes and other organs (when applicable), as described in American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 2009: 0 = melanoma in situ, not N1 or M1; IA = ≤1.0 mm without ulceration and a mitotic rate of <1/mm^2, not N1 or M1; IB = ≤1.0 mm with ulceration or a mitotic rate of ≥1/mm^2, or 1.01-2.0 mm without ulceration, not N1 or M1; Ix = ≤1.0 mm with unknown ulceration status or mitotic rate, not N1 or M1; II = 1.01-2.0 mm with ulceration or >2.0 mm, not N1 or M1; III-IV = N1 or M1.

trols) (**Figure**). Similarly, among men younger than 70 years at diagnosis, the relationship between PDE5 inhibitors and melanoma was only significant for stage 0 melanoma among men with a single filled prescription (eFigure 1 in the Supplement). However, there was no significant association between number of filled PDE5 inhibitor prescriptions and advanced stage melanoma.

Of 435 melanoma cases exposed to PDE5 inhibitors, 275 men (63%) had filled prescriptions for sildenafil and 224 men (51%) had filled prescriptions for vardenafil or tadalafil. The association with melanoma was similar for the 3 PDE5 inhibitors; sildenafil (OR, 1.14 [95% CI, 0.99-1.31]) and vardenafil or tadalafil (OR, 1.16 [95% CI, 0.99-1.37]). **Table 4** shows the results by number of filled prescriptions for sildenafil and vardenafil or tadalafil. Because some men used more than 1 type of PDE5 inhibitor, we performed a separate analysis of the 1110 men who only ever used sildenafil and 158 who only used vardenafil or tadalafil. There was a statistically significant association with melanoma in men who used sildenafil only (OR, 1.26 [95% CI, 1.08-1.48]) and vardenafil or tadalafil only (OR, 1.30 [95% CI, 1.08-1.57]).

To further assess the temporal aspect of the association between exposure and risk, we performed additional analyses. A significantly increased risk of melanoma was found only among men whose first prescription for PDE5 inhibitors was within 1 year prior to melanoma diagnosis (OR, 1.27 [95% CI, 1.09-1.48]); whereas, among men who began using PDE5 in-

Table 3. Odds Ratios of Malignant Melanoma by Number of Filled Prescriptions of PDE5 Inhibitor and Demographic Factors[a]

	No. (%)		Odds Ratio (95% CI)	
	Cases (n = 4020)	Controls (n = 19 972)	Crude	Adjusted
Filled prescriptions for PDE5 inhibitors				
None	3589 (89)	18 276 (92)	1 [Reference]	1 [Reference]
1	156 (4)	570 (3)	1.41 (1.17-1.69)	1.32 (1.10-1.59)
2-5	154 (4)	641 (3)	1.24 (1.03-1.48)	1.14 (0.95-1.37)
≥6	121 (3)	485 (2)	1.28 (1.04-1.58)	1.17 (0.95-1.44)
Comorbidity				
CCI 0	2788 (69)	13 215 (66)	1 [Reference]	1 [Reference]
CCI 1	637 (16)	3228 (16)	0.92 (0.84-1.02)	0.96 (0.87-1.05)
CCI 2+	595 (15)	3529 (18)	0.79 (0.71-0.87)	0.82 (0.74-0.90)
Marital status				
Not currently married	1233 (31)	7294 (37)	1 [Reference]	1 [Reference]
Married	2787 (69)	12 678 (63)	1.30 (1.21-1.40)	1.21 (1.12-1.30)
Educational level				
Low	1452 (36)	9059 (45)	1 [Reference]	1 [Reference]
Middle	1516 (38)	7020 (35)	1.36 (1.26-1.48)	1.28 (1.18-1.39)
High	1052 (26)	3893 (19)	1.70 (1.56-1.86)	1.47 (1.34-1.62)
Annual income, %				
1-25	768 (19)	5119 (26)	1 [Reference]	1 [Reference]
26-50	934 (23)	5108 (26)	1.23 (1.11-1.36)	1.21 (1.09-1.34)
51-75	1085 (27)	4964 (25)	1.50 (1.36-1.67)	1.36 (1.22-1.51)
76-100	1233 (31)	4781 (24)	1.84 (1.66-2.04)	1.54 (1.38-1.72)

Abbreviations: CCI, Charlson comorbidity index; PDE5, phosphodiesterase type 5.

[a] Complete case analysis.

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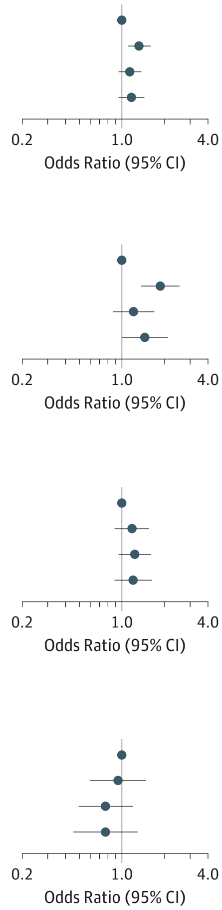
Figure. Filled Prescriptions for PDE5 Inhibitors and Risk of Melanoma by Stage

No. of Prescriptions[a]	No. (%) Cases	Controls	Odds Ratio (95% CI)
All stages			
None	3589 (89)	18 276 (92)	1.00 [Reference]
1	156 (4)	570 (3)	1.32 (1.10-1.59)
2-5	154 (4)	641 (3)	1.14 (0.95-1.37)
≥6	121 (3)	485 (2)	1.17 (0.95-1.44)

No. of Prescriptions[a]	No. (%) Cases	Controls	Odds Ratio (95% CI)
Stage 0			
None	1025 (87)	5376 (92)	1.00 [Reference]
1	63 (5)	158 (3)	1.86 (1.36-2.53)
2-5	48 (4)	187 (3)	1.21 (0.87-1.69)
≥6	41 (3)	136 (2)	1.45 (1.00-2.10)

No. of Prescriptions[a]	No. (%) Cases	Controls	Odds Ratio (95% CI)
Stage I			
None	1486 (88)	7599 (90)	1.00 [Reference]
1	68 (4)	283 (3)	1.18 (0.89-1.55)
2-5	77 (5)	292 (3)	1.23 (0.95-1.60)
≥6	61 (4)	234 (3)	1.20 (0.89-1.62)

No. of Prescriptions[a]	No. (%) Cases	Controls	Odds Ratio (95% CI)
Stage II-IV			
None	1034 (94)	5075 (93)	1.00 [Reference]
1	24 (2)	124 (2)	0.94 (0.60-1.48)
2-5	25 (2)	155 (3)	0.77 (0.50-1.20)
≥6	18 (2)	108 (2)	0.77 (0.46-1.29)



PDE5 indicates phosphodiesterase type 5.

[a] No. of prescriptions indicates No. of filled prescriptions for any PDE5 inhibitor.

Table 4. Odds Ratios of Malignant Melanoma in All Stages by Type of Phosphodiesterase Type 5 Inhibitor

No. of Filled Drug Prescriptions	No. (%) Cases (n = 4020)	Controls (n = 19 972)	Odds Ratio (95% CI) Crude	Adjusted
Sildenafil				
None	3747 (93)	18 828 (94)	1 [Reference]	1 [Reference]
1	118 (3)	482 (2)	1.23 (1.00-1.51)	1.17 (0.96-1.44)
2-5	98 (2)	407 (2)	1.23 (0.98-1.53)	1.16 (0.92-1.45)
≥6	57 (1)	255 (1)	1.12 (0.84-1.50)	1.06 (0.79-1.42)
Vardenafil or tadalafil				
None	3811 (95)	19 164 (96)	1 [Reference]	1 [Reference]
1	68 (2)	275 (1)	1.25 (0.95-1.64)	1.12 (0.85-1.47)
2-5	76 (2)	307 (2)	1.24 (0.96-1.60)	1.11 (0.86-1.44)
≥6	65 (2)	226 (1)	1.45 (1.10-1.92)	1.29 (0.97-1.71)

Adjusted for comorbidity, marital status, educational level, and annual income.

hibitors more than 1 year prior to diagnosis, there was no significant association (OR, 1.11 [95% CI, 0.94-1.31]) (eTable 2 in the Supplement).

Finally, 3327 men of 35 243 basal cell carcinoma cases (9%) had filled prescriptions for PDE5 inhibitors, as did 5364 of 70 468 controls (8%). There was an association between PDE5 inhibitors and basal cell carcinoma (adjusted OR, 1.19 [95% CI, 1.14-1.25]). The association between PDE5 inhibitors and basal cell carcinoma was significant for all types of PDE5 inhibitors, sildenafil (OR, 1.19 [95% CI, 1.12-1.25]) and vardenafil or tadalafil (OR, 1.18 [95% CI, 1.10-1.26]) (eTable 3 in the Supplement).

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Discussion

In a Swedish cohort of men, the use of PDE5 inhibitors was associated with a modest but significant increased risk of malignant melanoma. However, men with multiple filled prescriptions did not have a greater risk than those with a single prescription. In addition, the association was similar for short- and long-acting PDE5 inhibitors, and was significant for low-stage but not for high-stage melanoma. We also observed a significant association between use of PDE5 inhibitors with basal cell carcinoma. Overall, the pattern of association raises questions about whether this association is causal. Rather, the observed association may reflect confounding by lifestyle factors associated with both PDE5 inhibitor use and low-stage melanoma.

Li et al[2] previously reported an association between self-reported sildenafil use and melanoma risk among men in the Health Professionals Follow-up Study. In that study, recent use and ever use of sildenafil were associated with an increased risk of melanoma (HR, 1.84 [95% CI, 1.04-3.22] for recent use vs HR, 1.92 [95% CI, 1.14-3.22] for ever use). However, their results were based on only 142 melanoma cases of which 14 used sildenafil; whereas our risk estimates were based on 435 cases who had used any PDE5 inhibitor, and specifically 275 sildenafil users, resulting in more narrow confidence intervals for the risk estimates. Other important differences from our study are that Li et al did not differentiate between melanoma stages, which was possible in our study by use of detailed clinical information retrieved from the Swedish Melanoma Register, and their participants were asked about sildenafil use in a questionnaire in the year 2000, and no update on use of sildenafil or data on use of other PDE5 inhibitors were collected. By contrast, the relationship of all PDE5 inhibitors to melanoma was the primary research question for our study and we obtained complete data on all filled PDE5 inhibitor prescriptions from a nationwide prescription register, allowing us to examine cumulative exposure. Our overall risk estimate of 1.2 would translate to 7 additional cases of melanoma per 100 000 PDE5 inhibitor users based on the 2012 incidence of melanoma in Sweden of 35 melanoma cases per 100 000 men[14]; however, the age distribution in our cohort does not correspond to the general Swedish population, so the estimate may be biased. Furthermore, the estimate is based on the unlikely assumption that all men would have the same characteristics as men who had filled PDE5 inhibitor prescriptions in our study.

Following the study by Li et al, a recent editorial raised the question of whether sildenafil could have a role in the worse survival rate of melanoma in elderly men if it promotes melanoma cell invasion.[4] Indeed, melanoma cases diagnosed at an age older than 65 years have poorer survival compared with younger cases.[15] The observed disparities in survival by age and sex persisted even after adjustment for race/ethnicity, histologic subtype, anatomic site, stage at diagnosis, and depth. That notwithstanding, we found no association between sildenafil and other PDE5 inhibitors with advanced stage melanoma, suggesting that exposure to these drugs does not contribute to the previously observed differences in mortality by sex and age. Furthermore, Surveillance, Epidemiology, and End Results (SEER) data show an increase in the 5-year survival for melanoma cases diagnosed from 1999 through 2001 compared with earlier cases.[15] As sildenafil was approved for treatment of erectile dysfunction in 1998, this temporal trend provides additional ecologic evidence against a major role for PDE5 inhibitors in promoting invasiveness of melanoma.

Because sildenafil has a short half-life, and therefore a potentially less-prolonged effect on signaling pathways, we also studied other PDE5 inhibitors with a longer half-life to assess if there was a greater risk of aggressive melanoma for men using these drugs. However, even men with multiple filled prescriptions for vardenafil or tadalafil, with a longer half-life, did not have a significantly higher risk of melanoma.

In contrast to most other drugs in Sweden, PDE5 inhibitors are not subsidized. Correspondingly, we found an association between higher socioeconomic status and use of PDE5 inhibitors, similar to previous studies.[16,17] Also, a strong association between higher socioeconomic status and the risk of malignant melanoma has been documented.[18] Among PDE5 inhibitor users in our study, those diagnosed with melanoma had a higher socioeconomic status and a lower comorbidity burden than PDE5 inhibitor users not diagnosed with melanoma. Despite our efforts to adjust for variables related to socioeconomic status and health, it is possible that the observed relationship of PDE5 inhibitors with early stage melanoma reflects residual confounding from differences in lifestyle factors (such as leisure travel with ensuing sunburns) and health care seeking behavior.

Strengths of our study include the use of high-quality, population-based data from the Swedish national registries. Comprehensive linkages provided complete and detailed data including exact data on cumulative exposure by use of filled PDE5 inhibitor prescriptions in the Swedish Prescribed Drug Register with documented high capture and detailed melanoma stage from the Swedish Melanoma Register, in addition to information on socioeconomic factors and comorbidity. Our analysis also accounted for the potential confounding factor of prostate cancer, which is associated with both exposure[16] and outcome,[19] by censoring men at the date of prostate cancer diagnosis. Furthermore, our results were based on 30 times as many melanoma cases exposed to PDE5 inhibitors than in the previous study by Li et al (n = 14).[2] Our data also allowed assessment of possible associations between number of filled prescriptions, type of PDE5 inhibitor, and risk of melanoma by stage, which are all important factors when assessing the plausibility of a putative causal relationship between drug exposure and risk of cancer. Finally, the assessment of the association between basal cell carcinoma, a skin cancer not related to the implicated melanoma progression pathway, and use of PDE5 inhibitors provided a negative control.

Several limitations of the current study deserve mention. The median age at diagnosis of melanoma for US men is 64 years, whereas the median age of melanoma in our study population was 70 years because our analyses were based on a control population from the PCBaSe 3.0 database (selected from the general population as age-matched controls for men with

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prostate cancer). Thus, the proportion of younger men in our study was lower, which resulted in marginally lower power and wider confidence intervals for this subgroup. However, risk estimates in the subset analyses of men younger than 70 years yielded similar results to those in the full study group, further supporting the view that the age distribution was unlikely to materially affect the results. Thus, it is very unlikely that our sampling procedure introduced a selection bias. In addition, our classification of PDE5 inhibitor use was exclusively based on records of filled prescriptions. Prior studies from the United States have reported that a minority of men obtain PDE5 inhibitors online without a prescription,[20] which may also occur in Sweden, resulting in potential misclassification of exposure in some men. Finally, our data set did not include data on important melanoma risk factors such as skin type, history of sunburn, previous travel, and family history of melanoma.

Conclusions

In a Swedish cohort of men, the use of PDE5 inhibitors was associated with a modest but statistically significant increased risk of malignant melanoma. However, the pattern of association (eg, the lack of association with multiple filled prescriptions) raises questions about whether this association is causal.

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Study concept and design: Loeb, Folkvaljon, Lambe, Garmo, Ingvar, Stattin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Loeb, Folkvaljon.
Critical revision of the manuscript for important intellectual content: Loeb, Lambe, Robinson, Garmo, Ingvar, Stattin.
Statistical analysis: Folkvaljon, Garmo.
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Study supervision: Lambe, Garmo, Ingvar.

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